Translation

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PCT/JP2003/010871

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PH-007	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/JP2003/010871	International filing date (*day/month/year*) 27 August 2003 (27.08.2003)	Priority date (*day/month/year*) 27 August 2002 (27.08.2002)
International Patent Classification (IPC) or national classification and IPC A61K 45/00, 31/496, 9/14, 47/32, 47/34, A61P 1/04, 29/00, 31/04, 31/06, 31/18, 33/02, 35/00, 37/00, 37/04, 43/00, C07D 498/08		
Applicant TERADA, Hiroshi		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 15 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09 June 2004 (09.06.2004)	05 January 2005 (05.01.2005)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2003/010871

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is language of a translation furnished for the purpose of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ The international application as originally filed/furnished

☒ the description:

pages 1-7, 10-13, 16, 19-31, 33, 35, 37, 38, 40 , as originally filed/furnished

pages* 8, 15, 17, 18, 18/1, 32, 34, 36, 39 received by this Authority on 09 June 2004 (09.06.2004)

pages* 9, 9/1, 14 received by this Authority on 01 December 2004 (01.12.2004)

☒ the claims:

pages 4-13 , as originally filed/furnished

pages* _____ , as amended (together with any statement) under Article 19

pages* 1-3, 14 received by this Authority on 09 June 2004 (09.06.2004)

pages* 15-18 received by this Authority on 01 December 2004 (01.12.2004)

☒ the drawings:

pages 1/6-6/6 , as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2003/010871

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☒ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   See supplemental sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____ .

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

Invention 1: claims 1, 2, 4, 15 to 17 and parts of claims 3 and 5 to 14
Invention 2: claim 18 and parts of claims 3 and 5 to 14

Although inventions 1 and 2 are common to each other in relating to a remedy which induces the phagocytic activity of macrophages and is made to act on macrophages, a remedy inducing the phagocytic activity of macrophages and acting on macrophages had been publicly known at the time of the application of the present case, as described in the following document.

Accordingly, there is no technical relationship between these inventions 1 and 2 involving the same or corresponding special technical features, and these groups are not considered as a group of inventions so linked as to form a single general inventive concept.

Invention 1 relates to a remedy acting on macrophages and targeting diseases caused by a pathogen, while the invention 2 relates to a remedy acting on macrophages and targeting diseases not caused by such a pathogen.

Such being the case, it is recognized that the claims of the present international application have 2 inventions which do not relate to each other.

Document:
Sharma, R. et al., "Inhalable microparticles containing drug combinations to target alveolar macrophages for treatment of pulmonary tuberculosis", Pharm. Res., 2001, Vol. 18, No. 10, pages 1405 to 1410.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

The aforementioned document indicates that by treating macrophages with microparticles formed of poly(D-L lactic acid) having a remedy encapsulated therein, it is possible to increase the concentration of the remedy within the macrophage cell to a level greater than if macrophages are treated with said remedy in a dissolved form (page 1407, left column, line 15 from the bottom to line 11 from the bottom; page 1408, fig. 2, etc.).

The aforementioned document does not specifically mention that phagocytic activity of macrophages is actively induced, but poly(D-L lactic acid), a constituent ingredient of the microparticles of the aforementioned document, is listed in the description of this application (page 13, line 5) as satisfying the requirements of drug-carrying microparticles which may subject macrophages to phagocytosis, and in regard to the feature that the remedy encapsulated within the microparticles is rifampicin, the microspheres set forth in the aforementioned document are the same as the microparticles set forth in the description of this application, therefore the rifampicin-poly(D-L lactic acid) particles set forth in the aforementioned document are slightly different in terms of degree, but may be inferred as having the effect of "inducing phagocytic activity on macrophages" the same as the microparticles set forth in the description of this application, and this feature cannot be regarded as a difference.

In addition, in the written statement, the applicant does not back up the argument that the aforementioned assumption is irrational, and it is

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

obvious that the remedy encapsulated in the microparticles administered to the macrophages in the aforementioned document is "a remedy which acts on macrophages", therefore it is understood that the aforementioned document sets forth "a remedy which induces phagocytic activity of macrophages and acts on macrophages".

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP 03/10871

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	15-18	YES
	Claims	1-14	NO
Inventive step (IS)	Claims	15-18	YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	1-18	YES
	Claims		NO

2. Citations and explanations

Document 1: O'Hara, P. et al., "Respirable PLGA microspheres containing rifampicin for the treatment of tuberculosis: manufacture and characterization", Pharm. Res., 2000, Vol. 17, No. 8, pages 955 to 961

Document 2: Sharma, R. et al., "Inhalable microparticles containing drug combinations to target alveolar macrophages for treatment of pulmonary tuberculosis", Pharm. Res., 2001, Vol. 18, No. 10, pages 1405 to 1410

Document 3: Barrow, E.L. et al., "Use of microsphere technology for targeted delivery of rifampicin to Mycobacterium tuberculosis-infected macrophages", Antimicrobial Agents and Chemotherapy, 1998, Vol. 42, No. 10, pages 2682 to 2689

Document 4: Pushkarsky T. et al., "Lipopolysaccharide stimulates HIV-1 entry and degradation in human macrophages", J. Endotoxin. Res., 2001, Vol. 7, No. 4, pages 271 to 276

Document 5: Matsumoto, N. et al., "ONO-4007, an antitumor lipid A analog, induces tumor necrosis factor-alpha production by human monocytes only under primed state: different effects of

ONO-4007 and lipopolysaccharide on cytokine production", J. Pharmacol. Exp. Ther., 1998, Vol. 284, No. 1, pages 189 to 195

Document 1 cited in the international search report sets forth PLGA microspheres containing rifampicin and having a diameter of 1 to 5μm, and a method of treating tuberculosis which aims to subject said microspheres to phagocytosis by macrophages (see Abstract, etc.). Document 1 also indicates that PLGA having a molecular weight of 54,000 is used (see Table III).

Document 2 sets forth a method of treating tuberculosis, wherein poly (D-L lactic acid) microparticles containing rifampicin are used to attack tubercle bacilli which exist inside the macrophages (see Abstract, etc.).

Document 3 sets forth a method of treating tuberculosis, wherein rifampicin is introduced into PLGA microspheres, which are then delivered into the macrophages (see Abstract, etc.).

Document 4 cited in the written opinion indicates that lipopolysaccharide activates macrophages, making it possible to suppress the infection of macrophages by HIV-1 (see Abstract, etc.).

Document 5 indicates that ONO-4007 and lipopolysaccharides activate the discharge of TNF-α of macrophages, and have an antitumor effect (see Abstract, etc.).

Claims 1, 2, 4 and 6 to 14

(1) The invention set forth in claims 1, 2, 4 and 6 to 14 is disclosed in document 1, and therefore lacks novelty and does not involve an inventive step.

(2) The invention set forth in claims 1, 2, 4, 6, 7 and

12 to 14 is disclosed in document 2, and therefore lacks novelty and does not involve an inventive step.
(3) The invention set forth in claims 1, 2, 4, 6 to 9 and 12 to 14 is disclosed in document 3, and therefore lacks novelty and does not involve an inventive step.

Documents 1 to 3 do not mention a feature wherein the phagocytic activity of macrophages is induced, but the poly(D-L lactic acid) which is a constituent component of the microparticles in the aforementioned documents is listed in the description of this application (page 13, line 5) as satisfying the requirements of drug-carrying microparticles which may subject macrophages to phagocytosis, and in regard to the feature that the remedy encapsulated within the microparticles is rifampicin, the microparticles set forth in the aforementioned documents are the same as the microparticles set forth in the description of this application, therefore the rifampicin-poly(D-L lactic acid) microparticles set forth in the aforementioned documents are slightly different in terms of degree, but may be inferred as having the effect of "inducing phagocytic activity on macrophages", the same as the microparticles set forth in the description of this application, and this feature cannot be regarded as a difference.

In the response to the written opinion dated 1 December 2004, the applicant indicates that the microparticles set forth in the aforementioned documents and the microparticles of the embodiments of this application have different production methods and the molecular weight of the polymer used is different, but in the claims of this application, no production method for the microparticles is specified, and no molecular weight

of the polymer is specified, and if a molecular weight were mentioned, it would be within a similar range to that of the aforementioned documents, therefore this feature cannot be acknowledged as a difference. Moreover, referring to the description of this application, there is no disclosure indicating that phagocytic activity of macrophages is induced only when a specific production method is used, and as set forth in claim 10, PLGA of 1,500 to 150,000 may be used, therefore the molecular weight of the polymer used is understood to be able to be selected from a wide range, hence despite the aforementioned indication by the applicant, this does not prove the irrationality of the reasoning that the microparticles set forth in documents 1 to 3 induce phagocytic activity of macrophages.

Claims 2, 4 to 7 and 14

The remedy set forth in claim 2 of this application is described as having the characteristics: (A) induces phagocytic activity of macrophages and (B) induces the cell death of macrophages which hold pathogens, and the description of this application contains the specific example that a lipopolysaccharide is made to act on macrophages, and is used for the treatment of AIDS (see description, pages 36 to 38). Meanwhile, document 4 indicates that lipopolysaccharide is made to act on macrophages and is used to suppress infection to AIDS.

The aforementioned specific example given in the description of this application and the invention set forth in document 4 both have lipopolysaccharide as an active ingredient, and have the same applicable disease and the feature that the remedy is made to act on macrophages, therefore although not clearly stated in document 4, the invention set forth in document 4 may be assumed to have the aforementioned characteristics (A)

and (B).

Therefore the invention set forth in claim 2 and the invention set forth in claims 4 to 7 and 14 which refer back to said claim lack novelty and do not involve an inventive step in the light of document 4.

In the response to the written opinion dated 1 December 2004, the applicant indicates that the lipopolysaccharide set forth in document 4 is of *E. coli* bacteria origin, which is different from the polysaccharide in the embodiments of this application, but the claims of this application do not specify the active ingredient, hence this feature cannot be accepted as a difference. Moreover, in reference to the description of this application, it is not acknowledged to indicate that only a lipopolysaccharide originating from a specific bacteria has the aforementioned characteristics (A) and (B), therefore despite the aforementioned indication by the applicant, this does not prove the irrationality of the reasoning that the invention set forth in document 4 has the aforementioned characteristics (A) and (B).

Claims 3 and 5 to 7

The remedy set forth in claim 3 of this application is described as having the characteristics: (A) induces phagocytic activity of macrophages and (B) is made to act on macrophages in a functionally abnormal state, and the description of this application contains the specific example that a lipopolysaccharide is made to act on macrophages, and is used for the treatment of cancer (see description, pages 34 and 35). Meanwhile, document 5 indicates that lipopolysaccharide is made to act on macrophages and is used for the treatment of cancer.

The aforementioned specific example given in the

description of this application and the invention set forth in document 5 both have lipopolysaccharide as an active ingredient, and have the same applicable disease and the feature that the remedy is made to act on macrophages, therefore although not clearly stated in document 5, the invention set forth in document 5 may be assumed to have the aforementioned characteristics (a) and (b).

Therefore the invention set forth in claim 3 and the invention set forth in claims 5 to 7 and 14 which refer back to said claim lack novelty and do not involve an inventive step in the light of document 5.

In the written reply dated 1 December 2004, the applicant indicates that the lipopolysaccharide set forth in document 5 is of salmonella origin, which is different from the polysaccharide in the embodiments of this application, but the claims of this application do not specify the active ingredient, hence this feature cannot be accepted as a difference. Moreover, in reference to the description of this application, it is not acknowledged to indicate that only a lipopolysaccharide originating from a specific bacteria has the aforementioned characteristics (a) and (b), therefore despite the aforementioned indication by the applicant, this does not prove the irrationality of the reasoning that the invention set forth in document 5 has the aforementioned characteristics (a) and (b).

Claims 15 to 18

The invention set forth in claims 15 to 18 is novel and involves an inventive step in relation to documents 1 to 5.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Clarity and Support
Claims 1 to 7 and 14

Claims 1 to 3 of this application relate to remedies having desired characteristics such as "inducing the phagocytic activity of macrophages", "killing and exterminating all or part of the pathogens existing within the macrophages", "inducing cell death of macrophages which hold pathogens", or "acting on macrophages which are functioning abnormally".

The aforementioned claims of this application contain all types of remedies having the aforementioned characteristics, but only a very small portion of the claimed remedies are adequately supported by the description within the meaning of PCT Article 6, and disclosed within the meaning of PCT Article 5.

In addition, the aforementioned claims only specify the characteristics of remedies, and do not specify the active ingredients thereof at all. Taking into account the common general technical knowledge at the time of filing, it is not obvious how a remedy having the aforementioned characteristics would be prepared, therefore it is impossible to specify what substances would be contained in the aforementioned remedy, and the aforementioned claims of this application do not fulfill the requirement of clarity within the meaning of PCT Article 6.